17. The method of claim 14, wherein selecting one or more FK506 analogs comprises selecting one or more analogs of interest that bind FKBP-12 with a K_d of at least 100 μM.

18. The method of claim 14, wherein selecting one or more FK506 analogs comprises selecting one or more analogs irrespective of an activity of the one or more analogs in inhibiting FKBP-12 rotamase activity.

19. The method of claim 18, wherein selecting more or more FK506 analogs comprises selecting one or more analogs that do not substantially inhibit FKBP-12 rotamase activity when administered to a patient at dosage levels up to about 100 mg/kg body weight/day.

20. A method of identifying a FK506 analog that stimulates nerve cell growth, the method comprising:

screening FK506 analogs, selected from group consisting of the analogs of claim 13, for binding to FKBP-12;

selecting one or more FK506 analogs of interest that bind FKBP-12 with a K_d of at least 10 μM; and

performing additional assaying of one or more of the analogs of interest for activity in promoting nerve cell growth.

REMARKS

Claim 6 is pending. New claims 7-20 have been added by amendment.

Support for the claims is found at the following locations in the specification: claim 7 is supported at page 17, line 19; claims 8-10 at page 17, lines 9-17; claim 11 at page 17, lines 18 through 21; claim 12 at page 17; claim 13 at pages 6-16; claim 14 at page 17; claim 15 at page 26; claims 16, 17, 18, and 19 at page 17; and claim 20 at pages 6-17.

Claim 6 was rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Steiner et al., *Nature Medicine*, 3: 421-428, 1997 (Steiner). Applicants respectfully request reconsideration of the rejection in view of the following remarks.

In order for a reference to anticipate a claim, the reference must teach every element of the claim. Claim 6 is directed to a method of identifying a non-binding FK506 analog that stimulates nerve cell growth. Steiner does not teach *screening* a plurality of FK506 analogs for binding to FKBP-12, nor does Steiner teach *selecting* a FK506 analog that does not bind FKBP-12 for use in an additional assay for promoting cell growth. Since Steiner does not teach at least these elements of claim 6, that claim cannot be anticipated as alleged by the Office action.

Furthermore, Steiner does not establish a prima facie case of obviousness with respect to the claimed invention. Claim 6 involves selecting an FK506 analog that does *not* bind FKBP-12. Steiner teaches that FK506 analogs with *increased* ability to bind FKBP-12 are more strongly neurotrophic. For example, on page 422, in the last sentence of the only full paragraph in the right-hand column, Steiner states, "the potency of FK506 in stimulating neurite outgrowth is about the same as its potency in binding to FKBP-12 and inhibiting its rotamase activity, while L-685,818 is less potent in these actions, *corresponding to its lesser neurotrophic potency*" [italics supplied]. The data in this publication further leads Steiner to explicitly conclude, in the paragraph bridging pages 424-425, that there is "a parallel between affinities of drugs for FKBP-12 and their potencies in stimulating neurite outgrowth and inhibiting rotamase activity." It therefore would not be obvious to provide the claimed assay in which FK506 analogs are selected *even though* they do not bind to FKBP-12. One skilled in the art who read the findings and conclusions of Steiner would be led in the *opposite* direction from the claimed assay, and would consider FKBP-12 binding to be very important in selecting candidates for further testing. The prior art can not be said to make the claimed invention

obvious when it would motivate one skilled in the art to move in the opposite direction from the claimed method.

The method of claim 6 is a substantial advance in the field of finding drugs that promote nerve growth. As demonstrated by Steiner, prior to the present invention it had been thought that neurotrophic activity was proportional to binding to FKBP-12 (see quoted language above). This misconception limited the ability of researchers to find new agents that promoted nerve outgrowth, because researchers would not assay poor FKBP-12 binders for neurite outgrowth. Such assays were not performed because of the prevailing misconception that neurotrophic acitivty was "proportional" to FKBP-12 binding (as taught by the very Steiner reference cited in the Office action). Accordingly Steiner does not disclose or suggest the method of claim 6, and reconsideration of the rejection is requested.

Claim 7 adds the limitation that the compounds selected for the cell growth assays are selected irrespective of their ability to inhibit FKBP-12 rotamase. Steiner is again silent about performing such an assay, and therefore can not be said to anticipate the claimed method. Moreover, Steiner directly teaches away from the claimed screening method by explicitly stating that potency in stimulating neurite outgrowth is about the same as potency in inhibiting rotamase activity (with particular reference at page 422 to FK-506 and Table 1). It can not be said that Steiner suggests the claimed method in which agents are selected for further testing irrespective of their ability to inhibit rotamase activity. One skilled in the art who read Steiner would believe that it would be important to select agents exhibiting high inhibition of rotamase activity for further testing. To arrive at the present invention, one skilled in the art would have to disregard the teachings of Steiner (and others) that high rotamase inhibition was important to stimulating nerve cell growth.

The methods of claims 8-10 are directed to selecting FK506 analogs that bind FKBP-12 with particular affinities (as expressed by the K_d). The specifically claimed affinities are at levels that one skilled in the art would consider not to bind to FKBP-12, and which (in view of Steiner) would not be considered to have good neurite outgrowth potency. Use of these particular affinity levels of affinity in a method of screening for compounds that stimulate nerve cell growth is not disclosed in any of the cited references, and is therefore novel. Moreover, one skilled in the art would not have selected such compounds for further assays, as claimed, in view of the teaching of the very reference cited by the Office action that only compounds with high affinity for FKBP-12 were believed to have good neurotrophic potential.

Claims 11-12 are allowable for reasons already set forth.

Claim 13 sets forth the chemical structures of some of the FK506 analogs that could be tested in accordance an embodiment of the claimed method. Although these FK506 analogs may be suggested by other references, one skilled in the art would not have selected compounds with low FKBP-12 affinity or low rotamase activity, in view of the teaching (exemplified by Steiner) that a compound with these characteristics would not be expected to promote neurite outgrowth.

Claim 14 is a method of screening for an FK506 analog that stimulates nerve cell growth, by selecting analogs of interest that bind FKBP-12 with a K_d of at least 10 μM. This K_d is not disclosed in any cited reference in a method of identifying analogs that stimulate nerve cell growth, and the claim is therefore not anticipated. Moreover, Steiner teaches that much better binding to FKBP-12 would be desired when selecting analogs of interest. The method of claim 14 therefore goes against the teaching of the cited reference, and a prima facie case of obviousness has not been established with respect to this claim.

Claim 15 is directed to the particular assay in which the analog of interest undergoes testing to determine if it stimulates the growth of neurites from a cell. Claims 16-17 are directed to using a particular K_d in the screening method that is neither disclosed or suggested by the references. Claim 18 is directed to a screening method that is based upon rotamase activity. Claim 19 is directed to a screening method based upon both binding affinity and low rotomase inhibition. Claim 20 is directed to specifically enumerated FK506 analogs of interest.

If any matters remain to be resolved before a Notice of Allowance is issued, the Examiner is invited to telephone the undersigned patent attorney at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN CAMPBELL LEIGH & WHINSTON, LLP

By 

William D. Noonan, M.D.
Registration No. 30,878

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 226-7391
Facsimile: (503) 228-9446
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